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AR201-13629
Eastman Chemical Company
P.O. Box 511
Kingsport, Tennessee 37662

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Ms. Christine Todd Whitman, Administrator
US EPA
PO Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program

RE: HPV Chemical Challenge Program, AR-201

Dear Ms Whitman:

On behalf of Eastman Chemical Company, I am pleased to submit the test plan and robust summaries for 2-Butanone, 3-methyl- (CAS No.: 563-80-4). Please note that in our March 12, 1999 commitment letter we called this chemical methyl isopropyl ketone. My company had agreed to sponsor this chemical and provide the Agency with the enclosed information in the year 2003. However, due to the substantial amount of data that had been previously generated to understand the potential hazards of this chemical, we were able to complete our summarization ahead of schedule.

Enclosed with this letter is a computer diskette containing the test plan and robust summaries in Adobe Acrobat (.pdf) format. The HPV registration number for Eastman Chemical is

We understand this information will be posted on the internet for comments for a period of 120 days. Please forward comments to me at the above address.

Sincerely,

James A. Deyo D.V.M., Ph.D., D.A.B.T.
Technical Associate

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HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN
FOR
METHYL ISOPROPYL KETONE
(CAS NO.: 563-80-4)

PREPARED BY:
EASTMAN CHEMICAL COMPANY

February 14, 2002

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OVERVIEW

The Eastman Chemical Company hereby submit for review and public comment the test plan for methyl isopropyl ketone (MIPK; CAS NO.: 563-80-4) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of our company to use existing data on MIPK in conjunction with EPA-acceptable predictive computer models to adequately fulfill the Screening Information Data Set (SIDS) for the physicochemical, environmental fate, ecotoxicity test, and human health effects endpoints. We believe that in total these data are adequate to fulfill all the requirements of the HPV program without need for the conduct any new or additional tests.

Methyl isopropyl ketone is a water-white liquid that is manufactured to a high degree of purity. This ketone finds its primary uses in industrial applications where it is utilized as an intermediate in the synthesis of other chemicals and as an industrial solvent. It may also find some use as a solvent in coatings applications. Industrial work place exposure levels for this chemical have been established by the ACGIH, which set a TLV-TWA of 200 ppm (705 mg/m³).

TEST PLAN SUMMARY

CAS No. 563-80-4	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	-	Y	N	Y	N
Boiling Point	Y	-	-	Y	N	Y	N
Vapor Pressure	Y	-	-	Y	N	Y	N
Partition Coefficient	Y	-	-	Y	N	Y	N
Water Solubility	Y	-	-	Y	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y ¹	-	-	Y	N	Y	N
Biodegradation	Y	Y	-	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	-	Y	-	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	-	Y	-	N	Y	N
Toxicity to Aquatic Plants	Y	Y	-	-	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	-	Y	-	Y	Y	N
Repeated Dose Toxicity	Y	-	Y	-	Y	Y	N
Genetic Toxicity – Mutation	Y	Y	-	-	Y	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	-	-	Y	Y	N
Developmental Toxicity	Y	Y	-	-	Y	Y	N
Toxicity to Reproduction	Y	Y	-	-	Y	Y	N

1. A technical discussion has been provided.

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physicochemical

Melting point -	A value for this endpoint was obtained using a computer estimation model.
Boiling Point -	A value for this endpoint was obtained using a computer estimation model.
Vapor Pressure -	A value for this endpoint was obtained using a computer estimation model.
Partition Coefficient -	A value for this endpoint was obtained using a computer estimation model.
Water Solubility -	A value for this endpoint was obtained using a computer estimation model.

Conclusion: All end points have been satisfied by the utilization of data obtained from the various physical chemical data modeling programs within the EPIWIN suite (1). The results from the utilization of the models within this program have been noted by the Agency as acceptable in lieu of actual data or values identified from textbooks (2). No new testing is required.

B. Environmental Fate

Photodegradation -	A value for this endpoint was obtained using a computer estimation model.
Stability in Water -	A technical discussion describing the stability of ketones in water was provided.
Biodegradation -	This endpoint was satisfied through data derived from a study that followed an established OECD test guideline (301-D) and was conducted under GLP assurances.
Fugacity -	A value for this endpoint was obtained using the EQC Level III partitioning computer estimation model.

Conclusion: All endpoints have been satisfied using actual data or through the utilization of Agency-acceptable estimation models (2). A technical discussion was used to fulfill the endpoint assessing the stability of MIPK in water. In total, they are of sufficient quality to conclude that no additional testing is needed.

C. Ecotoxicity Data

Acute Toxicity to Fish -	This endpoint is filled by data from a well-conducted study with acceptable methods.
Acute Toxicity to Aquatic Invertebrates -	This endpoint is filled by data from a well-conducted study with acceptable methods.
Toxicity to Aquatic Plants -	This endpoint is filled by data from an OECD TG-201 study conducted under GLP assurances.

Conclusion: All endpoints have been satisfied with data from well-conducted studies using acceptable methodologies. While the data from the fish and Daphnia studies were not conducted under GLP assurances, their results are of sufficient quality to conclude that no additional testing is needed.

D. Toxicological Data

Acute Toxicity -	This endpoint is filled by data from studies conducted in rats that assessed the toxicity of MIPK following both oral and inhalation exposures. Although the studies did not follow standardized guideline protocols, they were conducted under GLP assurances. The quality of these studies was deemed as "reliable without restrictions".
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Repeat Dose Toxicity -	This endpoint is filled by data from an inhalation study of 28-days duration. The protocol followed was comparable to that of an OECD-412 guideline and the study was conducted under GLP assurances. The quality of this study was deemed as “reliable without restrictions”.
Genetic Toxicity Mutation -	This endpoint is filled with a study that followed OECD guideline #471 and was conducted under GLP assurances. This study utilized <i>Salmonella typhimurium</i> (strains TA 98, 100, 1535, 1537, and 1538) and <i>Escherichia coli</i> (strain WP2uvrA). The quality of this study was deemed as “reliable without restrictions”.
Aberration -	This endpoint is filled with data from an <i>in vitro</i> study using Chinese hamster ovary (CHO) cells that followed OECD guideline #473 and was conducted under GLP assurances. The quality of this study was deemed as “reliable without restrictions”.
Developmental Toxicity -	This endpoint is filled by data from an inhalation exposure study in rats that followed OECD guideline #421 and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential. The quality of this study was deemed as “reliable without restrictions”.
Reproductive Toxicity -	This endpoint is filled by data from an inhalation exposure study in rats that followed OECD guideline #421 and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential. The quality of this study was deemed as “reliable without restrictions”.
Conclusion:	All endpoints have been satisfied with data from studies whose methods followed established OECD guidelines, or utilized methods that were very similar and scientifically appropriate. All studies were conducted under GLP assurances. In total they were all of sufficient quality to deem them as “reliable without restrictions” and to conclude that no additional testing is needed.

SIDS DATA SUMMARY

Data assessing the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for MIPK were all obtained from computer estimation models within the EPIWIN suite. These data indicate that MIPK is a liquid at room temperature with a relatively low vapor pressure. It has a low estimated octanol to water partition coefficient and accordingly is quite soluble in water despite being classified as “slight”.

The assessment of the environmental fate endpoints (photodegradation, biodegradation, stability in water, and fugacity) was completed through the use of an actual study, acceptable estimation modeling programs, and a technical discussion. As a result of its solubility in water and relatively low volatility, fugacity estimations predict that MIPK will distribute primarily to soil and water. A technical discussion has been provided that indicates this ketone is not likely to undergo hydrolysis. The available biodegradation data indicate MIPK is likely to be readily degraded in the environment. Its primary use is in industrial applications; environmental releases will primarily occur through evaporative emissions where MIPK is expected to degrade in the atmosphere at a moderate to slow rate.

The potential toxicity of MIPK to fish, Daphnia, and algae were determined through well-conducted studies. The results of these studies demonstrate fish and Daphnia are not sensitive species with both having a NOEC >100 mg/L. However, the NOEC of MIPK on algal growth was determined to be 14.8 mg/L. Based on these data MIPK would be classified as “harmful to aquatic organisms” according to the European Union’s labeling directive but

would be classified in a “moderate concern level” according to the U.S. EPA’s assessment criteria. The potential for exposure to aqueous environments is unlikely due to its primary uses in industrial applications. Furthermore, MIPK is noted as being readily biodegradable.

The potential to induce toxicity in mammalian species following acute oral and inhalation exposures is very low. The oral LD₅₀ value in rats is 3,078 mg/kg, while data from an inhalation study in rats yielded an LC₅₀ of 6,377 ppm (22,464 mg/m³) following a 6-hour exposure. Data from a repeat inhalation exposure study in rats at levels of 750, 1,500, and 3,000 ppm (2,642, 5,284, and 10,569 mg/m³) for a duration of 28-days indicated the material was well tolerated with minimal evidence of toxicity. No NOEL was established in this study as clinical signs of toxicity (narcosis and lethargy) were seen at all levels. However, they rapidly diminished after exposure cessation and the primary effect noted was a non-specific decrease in body weight at the highest two exposure levels. A possible cause of this decreased weight gain could have been a decrease in food consumption related to the time needed to recover from the exposure-induced depression. Furthermore, there was minimal evidence of any target organ toxicity based on a lack of changes in absolute organ weights and normal histological appearances (males showed evidence of hyaline droplets). Hyaline droplet formation seen in the kidneys of males is not relevant to humans. Results from mutagenicity and chromosomal aberration studies indicate this material is not genotoxic. Developmental and reproductive toxicity endpoints were assessed simultaneously through the conduct of a developmental/reproductive toxicity screening inhalation study in rats that followed OECD test guideline #421. Results from this study indicate MIPK is not likely to induce either type of effect. No NOAEL was determined for maternal effects as signs of toxicity (reductions in general activity levels) were noted in all treated groups during the inhalation exposures. In addition, lower mean body weight gain and feed utilization was noted in all three treatment groups. The NOAEL for fetal effects was 1 mg/L (1,000 mg/m³).

In conclusion, an adequate assessment and summarization of all the Screening Information Data Set (SIDS) endpoints has been completed to satisfy the requirements of the HPV program without need for the conduct of any new or additional tests. This data set consists of results from studies conducted on MIPK that either followed established protocols under GLP assurances or scientifically acceptable procedures to assess the various endpoints. Where appropriate, some endpoints have been fulfilled through the utilization of data from modeling programs accepted by the EPA. The summarized data indicate that this chemical, when used appropriately, should constitute a low risk to both workers and the general population.

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance (3) and the systematic approach described by Klimisch *et al.* (4). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation (5). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

- (1) **Reliable without Restriction:** Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.
- (2) **Reliable with Restrictions:** Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.
- (3) **Not Reliable:** Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.
- (4) **Not Assignable:** Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

REFERENCES

1. EPIWIN, Version 3.01, Syracuse Research Corporation, Syracuse, New York.
2. US EPA. (1999). The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.
3. USEPA (1998). 3.4 Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.
4. Klimisch, H.-J., Andreae, M., and Tillmann, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacol.* 25:1-5.
5. USEPA. 1999. Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.

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I. General Information

CAS Number: 563-80-4
Name: 2-Butanone, 3-methyl-
3-Methylbutanone
3-Methyl-2-butanone
2-Acetylpropane
2-Methyl-3-butanone
2-Methylbutan-3-one
Isopropyl methyl ketone
Methyl isopropyl ketone
MIPK

II. Physical-Chemical Data**A. Melting Point**

Test Substance Test substance: Remarks:	MIPK
Method Method: Remarks:	Estimation
Results Melting point value: Remarks:	-79.46 °C
References	MPBPWIN v1.31; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.01, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

B. Boiling Point

Test Substance Test substance: Remarks:	MIPK
Method Method: Remarks:	Estimation Method was noted to have been an adaptation of Stein & Brown
Results Boiling point value: Remarks:	80.27 °C
References	MPBPWIN v1.31; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.01, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

C. Vapor Pressure

Test Substance Test substance: Remarks:	MIPK
Method Method: Remarks:	Estimation Mean of Antoine and Grain methods
Results Vapor pressure value: Temperature: Remarks:	95.5 mmHg 25 °C
References	MPBPWIN v1.31; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.01, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

D. Partition Coefficient

Test Substance Test substance: Remarks:	MIPK
Method Method: Remarks:	Estimation
Results Log K _{OW} : Remarks:	0.67 The EPIWIN database had a listed value of 0.84.
References	KOWIN v1.63; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.01, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

E. Water Solubility

Test Substance Test substance: Remarks:	MIPK
Method Method: Remarks:	Estimation
Results Value: Temperature: Description: Remarks:	2,436 mg/L 25 °C Slight (1-10 g/L) A K_{ow} of 0.84 was used in the estimation
References	WSKOW v1.33; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.01, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

III. Environmental Fate Endpoints

A. Photodegradation

Test Substance Test substance: Remarks:	MIPK
Method Method: Test type: Remarks:	Estimation Atmospheric oxidation
Results Temperature: Hydroxyl radicals reaction OH Rate constant: Half-life Ozone reaction: Remarks:	25 °C $2.6178 \times 10^{-12} \text{ cm}^3/\text{molecule-sec}$ 4.086 Days (12-hr day; $1.5 \times 10^6 \text{ OH}/\text{cm}^3$) No ozone reaction estimation
Conclusions	Material is oxidized by atmospheric hydroxyl radicals at a slow rate.
Data Quality Remarks:	
References	AopWin v1.88; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.01, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

B. Stability in Water

Reactivity of Selected Ketones With Water

This report has been prepared Dr. Paul Worsham of Eastman Chemical to document the known chemistry relevant to the stability of selected ketones in aqueous solution. The specific ketones addressed in this document are methyl propyl ketone (MPK; CAS# 107879), methyl isopropyl ketone (MIPK; CAS# 563804), methyl isoamyl ketone (MIAK; CAS# 110123), and methyl n-amyl ketone (MAK; CAS#110430).

Of particular concern in the evaluation of the stability of organic compounds in aqueous solution is the potential for hydrolysis. Hydrolysis is the reaction between water and an organic substrate resulting in the cleavage of existing chemical bonds and subsequent or simultaneous formation of new chemical bonds to form a different chemical compound. Typically, hydrolysis reactions involve incorporation of a water molecule into the structure of the reaction products. For organic substances that participate in hydrolysis reactions, various kinetic methods can be used to monitor the changes in concentration of reactants and determine the rate of transformation of the original substrate into reaction products. OECD Guideline 111 describes one such procedure for measuring the hydrolysis rate of water-soluble substrates as a function of pH. Substrates that exhibit high rates of hydrolysis are considered unstable in an aqueous environment.

Ketones as a class, and specifically the ketones identified above, do not participate in hydrolysis reactions. These ketones do not possess labile leaving groups that can be displaced by the nucleophilic attack of a water molecule, as is required in the mechanism of many hydrolysis reactions. Thus, it would not be meaningful to attempt to measure a hydrolysis rate using a protocol such as OECD Guideline 111.

Certain ketones may add water to form a hydrate under aqueous conditions, especially in the presence of mild acid; but, this addition is an equilibrium reaction that is reversible upon a change in water concentration, and the reaction ultimately leads to no permanent change in the structure of the ketone substrate.^{1,2}

A significant property of most ketones is that the hydrogen atoms on the carbons next to the carbonyl group are relatively acidic when compared to hydrogen atoms in typical hydrocarbons. Under strongly basic conditions these hydrogen atoms may be abstracted to form an enolate anion. This property allows ketones, especially methyl ketones such as the four ketones above, to participate in condensation reactions with other ketones and aldehydes. This reaction is called an aldol reaction and generates a higher molecular weight ketone having a hydroxyl group at the site of attack by the enolate anion. This type of condensation reaction is favored by high substrate concentrations and high pH (greater than 1 wt% NaOH). It is conceivable that some alkyl ketones, especially methyl ketones, could participate in aldol reactions in dilute aqueous solution at pH of 9 or higher. But, these reactions would be expected to be slow at ambient temperature, and the equilibrium for condensation of two ketones is unfavorable for aldol product formation³. Also, formation of the aldol product is reversible unless dehydration of the aldol occurs. Dehydration of an aldol intermediate in aqueous solution at ambient temperature also would be very slow.

Based on the properties of ketones described above one must conclude that MPK, MIPK, MIAK, and MAK are not subject to hydrolysis, but may participate in other transformations that convert the ketone to higher molecular weight compounds. These reactions would be expected to be very slow at mild temperatures and moderate pH. Therefore, it is my conclusion that MPK, MIPK, MIAK, and MAK should be considered stable in aqueous solution at temperatures and pH levels relevant to environmental and human exposure.

References:

- (1) Bell and Clunie, *Trans. Faraday Soc.*, **48**, 439, (1952).
- (2) Cohn and Urey, *J. Am. Chem. Soc.*, **60**, 679 (1938).
- (3) March, J., ed. "Advanced Organic Chemistry", 3rd edition, p. 831, John Wiley & Sons, New York, 1985.

C. Biodegradation

Test Substance	
Test substance:	MIPK
Remarks:	Purity was 99.6%
Method	
Method:	OECD TG-301D
Test type:	Ready Biodegradability by the Closed Bottle Method
GLP:	Yes
Year:	2001
Contact time:	28-Days
Inoculum:	Activated sludge collected from Wareham, MA wastewater treatment plant
Remarks:	Benzoic acid at 10 mg/ml was used as a reference control. MIPK was assessed at a nominal concentration of 2.5 mg/L. Test vessels of 300ml BOD bottles were prepared per treatment (reference, test substance and inoculum blank), two each for Day 0 and three per sampling interval (Days 7, 14, 21, and 28). After the bottles were filled they were closed and wrapped in tin foil.
Results	
Degradation % at test end:	85% (>60% by Day 14)
Classification:	Readily biodegradable
Remarks:	Benzoic acid reference was degraded 84%. The temperature of the environment ranged from 20-24 °C. Dissolved oxygen concentrations in the control blank ranged from 9.1 mg/L on Day 0 to 7.8 mg/L on Day 28.
Conclusions	Material is considered readily biodegradable under the conditions of this test.
Data Quality	
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Methyl Isopropyl Ketone – Determination of the Ready Biodegradability of a Test Substance by the Closed Bottle Method; Springborn Laboratories, Inc Wareham, MA Study No. 1852.6178, August 7, 2001.
Other	

D. Transport between Environmental Compartments (Fugacity)

Test Substance Test substance: Remarks:	MIPK										
Method Test type: Model used: Remarks:	Estimation Level III Fugacity Model; EPIWIN: EQC from Syracuse Research Corporation										
Results Model data and results: Estimated distribution and media concentration (levels II/III): Remarks:	<table><tr><th colspan="2">Concentration (%)</th></tr><tr><td>Air</td><td>12.2</td></tr><tr><td>Water</td><td>49.4</td></tr><tr><td>Soil</td><td>38.3</td></tr><tr><td>Sediment</td><td>0.0633</td></tr></table> <p>Physical chemical values and estimated half-life values utilized in this model were default values or obtained from the EPIWIN program.</p>	Concentration (%)		Air	12.2	Water	49.4	Soil	38.3	Sediment	0.0633
Concentration (%)											
Air	12.2										
Water	49.4										
Soil	38.3										
Sediment	0.0633										
Data Quality Remarks:											
References	Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.01, Syracuse Research Corporation, Syracuse, New York 13210. The Level III model incorporated into EPIWIN is a Syracuse Research Corporation adaptation of the methodology described by Mackay <i>et al.</i> 1996; <i>Environ. Toxicol. Chem.</i> 15(9) , 1618-1626 and <i>Environ. Toxicol. Chem.</i> 15(9) , 1627-1637.										
Other											

IV. Ecotoxicity

A. Acute Toxicity to Fish

<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Analytical monitoring: Exposure period: Remarks:</p> <p>Results Nominal concentration: Endpoint value: Biological observations:</p> <p>Statistical methods: Remarks:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>MIPK Purity was not available</p> <p>Other Static No 1988 Fathead minnow (<i>Pimephales promelas</i>) Yes; Exposure solutions, temperature, pH, dissolved oxygen 96-Hour Water was filter-treated lake water with residual chlorine chemically removed. 10 fish per concentration level were used. Test was conducted in replicate at each concentration in glass containers. The biological loading was kept below 1.0 g wet wt./L. Exposure solutions were submitted for temperature, dissolved oxygen, and pH concentration determinations at 0, 24, 48, 72, and 96 hrs. Observations for stress and mortality were conducted at 0, 6, 24, 48, 72, and 96 hours.</p> <p>100 mg/L LC₅₀ >100 mg/L All control behavior was normal. One exposed fish was noted to exhibit depressed activity at 24-hours, all were normal at 48 hours, one was found dead between the 48 and 72 hour period and one was noted to be near death at 96-hours.</p> <p>NA; Only one mortality was noted out of 20 Exposure temperature ranged from 20-21 °C, pH ranged from 7.7 to 8.4, and dissolved oxygen ranged from 5.4 to 8.9 mg/L. Solutions were gently aerated at 72 hours when the oxygen levels became depressed.</p> <p>The LC₅₀ value indicates that the test substance would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria.</p> <p>Reliable with restrictions Study lacked some basic information as well as data indicating test material purity and analytical conformation of test concentrations.</p> <p>An Acute Aquatic Effects Test with the Fathead Minnow (<i>Pimephales promelas</i>); Environmental Sciences Section, Health and Environment Laboratories, at Eastman Kodak Company, Rochester, NY; HAEL No. 88-0008; June 8, 2000.</p>
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B. Acute Toxicity to Aquatic Invertebrates

Test Substance Test substance: Remarks:	MIPK Purity was not available
Method Method: Test type: GLP: Year: Species/strain: Analytical monitoring: Exposure period: Remarks:	Other Acute immobilization, Static No 1988 Daphnid/ <i>Daphnia magna</i> Yes; Exposure solutions, temperature, pH, dissolved oxygen 48-Hour Water was filter-treated with residual chlorine chemically removed. 10 Daphnids per dose level were used. Test was conducted in replicate at each concentration in glass containers. Exposure solutions were submitted for temperature, dissolved oxygen, and pH concentration determinations at 0, 24, and 48 hrs. Observations for stress and mobility were conducted at 0, 6, 24, and 48 hours.
Results Nominal concentration: Endpoint value: Biological observations: Statistical methods: Remarks:	100 mg/L EC ₅₀ (48-hr) >100 mg/L The <i>Daphnia</i> exhibited behavior comparable to controls at 24 hours, but at 48-hours many were noted to be positioned at the surface. NA; No significant differences in immobility were noted between treated and control Daphnids. Exposure temperature ranged from 20-21 °C, pH ranged from 8.0 to 8.4, and dissolved oxygen ranged from 6.8 to 8.9 mg/L.
Conclusions	The EC ₅₀ value indicates that the test substance would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria.
Data Quality Reliability: Remarks:	Reliable with restrictions Study lacked some basic information as well as data indicating test material purity and analytical conformation of test concentrations.
References	An Acute Aquatic Effects Test with the Daphnid (<i>Daphnia magna</i>); Environmental Sciences Section, Health and Environment Laboratories, at Eastman Kodak Company, Rochester, NY; HAEL No. 88-0008, June 8, 2000
Other	

C. Toxicity to Aquatic Plants

Test Substance	
Test substance:	MIPK
Remarks:	Purity was 99.6%
Method	
Method:	OECD: TG-201
Test type:	Growth inhibition of algae
GLP:	Yes
Year:	2001
Species/strain:	<i>Selenastrum capricornutum</i>
Endpoint basis:	Cell concentrations (biomass) and growth rate
Exposure period:	72-hours
Analytical procedures:	Temperature, light intensity, rpm, and test substance concentration were
Remarks:	assessed at the 0, 24, 48, and 72 hours. The pH was assessed at time 0 and after 72 hours.
Results	
Nominal concentration:	7.8, 15.6, 31.3, 62.5, and 125.0 mg/L
Measured concentration:	4.1, 7.5, 14.8, 29.5, and 61.8 mg/L (geometric mean over all time points)
Endpoint value:	The estimated E_bC_{50} (0-72 hr) was 34.0 mg/L; the E_rC_{50} (0-72 hr) was
NOEC:	44.2 mg/L
Biological observations:	The 72 hr NOEC was estimated to be 14.8 mg/L
Was control response	No deformed cells were noted
satisfactory:	Yes (culture concentrations increased by a factor of 93-fold)
Statistical methods:	EC_{50} and NOEC values were determined through use of SAS statistical software
Remarks:	program AL_ACUTE (Ver. 2.2).
	A mean illumination of 719.5 foot-candles was maintained. The mean culture
	temperature was 24°C and pH ranged from 7.5 to 9.0. Cultures were oscillated
	at 100 rpm. The significant loss (up to 78.2% over the course of the study) in
	test material was attributed to volatilization. No protocol deviations were noted.
Conclusions	
	The 72-hour E_bC_{50} and E_rC_{50} values indicate that, based on this study, the test
	substance would be classified as “harmful to aquatic organisms” according to
	the European Union’s labeling directive and would be classified in a “moderate
	concern level” according to the U.S. EPA’s assessment criteria.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP
	assurances.
References	
	A Growth Inhibition Test with the Alga, <i>Selenastrum capricornutum</i> ;
	Environmental Sciences Section, Health and Environment Laboratories,
	Eastman Kodak Company, Rochester, NY; Laboratory Project ID: EN-512-
	903146-A; July 11, 2001.
Other	

V. Toxicological Data

A. Acute Toxicity

<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Sex: Animals/dose: Vehicle: Route of exposure: Remarks:</p> <p>Results Value: Deaths at each dose: Remarks:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>MIPK Purity unknown</p> <p>Acute lethality; Other LD₅₀ estimate Yes 1988 Rat/Crl:CD® (SD)BR Both 5 Undiluted Oral Animals weighing 125-140 g (males) and 130-148 g (females) were administered doses of MIPK at a rate of 1,250, 2,500, and 5000 mg/kg. Animals were monitored for 14 days before being euthanized, dissected, and examined grossly. The LD50 estimate was determined by the Weil method.</p> <p>LD₅₀ = 3,078 mg/kg (both sexes) 1,250: none; 2,500: 2 (1/sex); 5,000: 10 (5/sex) 1,250 and 2,500 mg/kg: Clinical signs seen included slight to moderate weakness and ataxia in all animals shortly after dosing. All recovered after 24 hours and gained weight. None exhibited any gross pathological changes at necropsy. 5,000 mg/kg: Clinical signs included slight to severe weakness, ataxia, and prostration in all animals on day of dosing, with 2 males and 3 females dying within 4 hours. The remaining animals were found dead on next day. The only gross observation noted at necropsy was seen in those animals that died very shortly after dosing and consisted of test material in the GI tract. The exact cause of death was not determined in any animal.</p> <p>Material is considered slightly toxic</p> <p>Reliable without restrictions Although test article purity was not given, this is a well-documented study conducted under GLP assurances.</p> <p>Acute toxicity of methyl isopropyl ketone, Toxicological Sciences Laboratory, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; HAEL No. 88-0008, May 19, 1988.</p>
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<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Sex: Animals/sex/dose: Route of exposure: Remarks:</p> <p>Results Value: Deaths at each dose: Remarks:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>MIPK Purity was >98%</p> <p>Acute lethality; Other LC₅₀ estimate Yes 1987 Rat/Crl:CD® (SD)BR Both 5 Inhalation Males were 7 weeks old and weighed 252 g, while females were 9 weeks of age and weighed 201 g on average. Animals were exposed to MIPK using whole-body chambers for 6 hours at nominal concentrations of 0, 4,000, 6,000, or 9,000 ppm. Actual measured levels were 4,026, 5,708, and 8,270 ppm. After exposure, animals were monitored for clinical observations and weight change for 14-days prior to being euthanized.</p> <p>LC₅₀ (6-hr) = 6,377 ppm (22,464 mg/m³) average of both sexes 4,000: 0/10; 6,000: 3/10 (1M, 2F); 9,000: 9/10 (5M, 4F) During the exposure phase (Day 0) all animals in all groups exhibited severe CNS depression, lacrimation and dose-dependent hypoventilation. After exposure on Day 0 all animals exhibited minor lethargy to severe CNS depression and minimal to severe lacrimation. Sialorrhea was exhibited in one female exposed to 4,000 ppm. One of each sex at the 6,000 ppm level and all 5 males and 2 females exposed to 9,000 ppm died shortly after exposure on Day 0. The next day, one female each from the mid and high groups continued to show lethargy, poor body condition, and lacrimation. Piloerection was noted in all surviving animals in the 6,000 ppm group. Two females in the 9,000 ppm group died on Day 1. On Day 2, one female in the 6,000 ppm group died; the sole surviving female in the 9,000 ppm group showed lethargy, piloerection, gait disturbance, and ataxia. On Day 3 this animal had weight loss in addition to an unkempt and yellowed haircoat. Weight gains in those surviving exposure were minimal to negative during Day 1-3 but after three days all showed sustained gains and by Day 14 all groups were comparable to controls. The exact cause of death was not determined in any animal and no gross pathological changes were seen in any animal dying prematurely or at Day 14.</p> <p>Reliable without restrictions This is a well-documented study conducted under GLP assurances.</p> <p>Acute inhalation toxicity study of methyl isopropyl ketone in the rat, Toxicological Sciences Laboratory, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; HAEL No. 86-0157, June 8, 1987.</p>
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B. Repeated Dose Toxicity

Test Substance	
Test substance:	MIPK
Remarks:	Purity was 99.4%
Method	
Method:	Comparable to OECD-412, and EEC Annex V.B.8
Test type:	Repeated exposure
GLP:	Yes
Year:	1981
Species/strain:	Rat/CRL:CD [®] (SD)BR
Route of exposure:	Inhalation
Duration of test:	28-Days
Exposure levels:	0, 750, 1,500, 3,000 ppm
Sex:	Both
Exposure period:	6 hours/day
Frequency of treatment:	5 days/week
Control group and treatment:	Controls were exposed to room air.
Post-exposure observation period:	None
Remarks:	Rats (5/sex/dose) weighing 199 g (M) and 181 (F) were randomly assigned to each of the exposure groups. Animals were exposed using whole-body chambers and given feed <i>ad libitum</i> only during non-exposure periods. Body weights were recorded on Days 0, 4, 7, 14, 21, and 28 and clinical observations were made before and after exposure each day. At necropsy, complete hematology and clinical chemistry parameters were assessed and a full assortment of tissues was harvested for histological assessment.
Results	
NOAEL:	A NOAEL was not determined due to presence of clinical effects during the exposure period. These effects rapidly dissipated during the post exposure period. No evidence of systemic toxicity was seen at 750 ppm (2,642 mg/m ³) and the LOAEL (based on weight loss) was 1,500 ppm (5,284 mg/m ³).
Actual exposure levels:	730, 1,488, 2,958 ppm

<p>Toxic responses by dose:</p>	<p>No mortalities were observed in this study. Mean body weights were, in general, decreased in a dose dependent manner with it being statistically significant at Day 28 in the 1,500 and 3,000-ppm animals only. Both sexes exhibited dose-dependent lethargy (all dose levels) or moderate to severe narcosis (3,000 ppm) during most exposures. Excessive lacrimation was noted in all animals during the first exposure and then once thereafter in the 750 ppm group or on several occasion in one or more animals at the two higher levels. Animals in the 3000 ppm group also exhibited gait disturbances. Sialorrhea was noted on in 1-2 animals across all dose levels on occasion. All clinical signs rapidly diminished post-exposure and were not observed in the next day's pre-exposure observations. No changes in hematology or clinical chemistry parameters were observed that were considered to be related to test article exposure. Trends for an increase in several organ weights were noted, but statistical significance was only seen when compared on a relative to body weight basis and only at the two highest dose levels where reductions in body weight was also manifested. Absolute organ weight increases were noted in the adrenal gland of males and the livers of females, both only occurred at the highest exposure level and were seen in both sexes. Males at all levels showed evidence of hyaline droplet formation with a significant increase in its severity associated at the 1500 and 3000 ppm level. No histopathological changes were seen in females at any exposure level.</p>
<p>Statistical methods:</p>	<p>All continuous data were evaluated using computer generated statistical test: Bartlett's Test, One-way ANOVA, and Duncan's multiple range test. In cases of unequal variances a two-tailed t-test was employed. Selected pathology data were evaluated using contingency table analysis. Tests of independence and measures of association were done on two-way tables using the likelihood ratio Chi-square statistic. Multi-way tables were analyzed using log-linear models and the likelihood ratio Chi-square statistic. Significant effects were further examined using Dunnett's t-test.</p>
<p>Remarks:</p>	
<p>Conclusions</p>	<p>In general test material was well tolerated with the primary effect being a non-specific decrease in body weight at the highest two doses. A possible cause of this could be a decrease in food consumption related to the time needed to recover from the exposure-induced depression effects. (Unfortunately food intake was not measured to validate this hypothesis.) Although clinical signs of toxicity were seen at all levels, they rapidly diminished after exposure cessation. Furthermore, there was minimal evidence of any target organ toxicity based on changes in absolute organ weights and normal histological appearances. Hyaline droplet formation is not relevant to humans.</p>
<p>Data Quality Reliability: Remarks:</p>	<p>Reliable with restrictions This study was conducted using established protocols and GLP assurances.</p>
<p>References</p>	<p>Four Week Inhalation Toxicity Study of Methyl Isopropyl Ketone in the Rat. Toxicological Sciences Laboratory, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; HAEL No. 88-0008, June 28, 1989.</p>
<p>Other</p>	

C. Genetic Toxicity – Mutation

Test Substance	
Test substance:	MIPK
Remarks:	Purity was 99.6%
Method	
Method:	OECD: TG-471
Test type:	<i>In vitro</i> mutagenicity
GLP:	Yes
Year:	2001
Species/strain:	<i>Salmonella typhimurium</i> /TA98, 100, 1535, 1537, and <i>Escherichia coli</i> /WP2uvrA
Metabolic activation:	Yes; Aroclor 1254-induced SD rat liver S9
Concentration tested:	Maximum concentration tested was 5000 ug/plate
Remarks:	Positive controls (benzo[a]pyrene, 2-aminoanthracene, 2-nitrofluorene, sodium azide, 2-aminoanthracene, ICR-191, and 4-nitroquinoline-N-oxide) were run concurrently. DMSO was used as a vehicle control.
Results	
Result:	No positive responses were induced in any of the tester strains
Cytotoxic concentration:	>5000 ug/plate (no evidence of cytotoxicity was seen)
Precipitation concentration:	No precipitate was noted at the highest concentration tested.
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical Methods:	Mean number of revertants and standard deviations were calculated. Various criteria were established to constitute a valid assay and a positive response was indicated by a 2-3 fold increase in mean revertant number dependent on the bacterial tester strain.
Remarks:	All criteria for a valid study were met.
Conclusions	Material was not genotoxic under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Covance Laboratories Inc., Vienna, VA; Study No.: 23080-0-409OECD; February 7, 2002.
Other	

D. Genetic Toxicity – Chromosomal Aberrations

Test Substance Test substance: Remarks:	MIPK Purity was 99.6%
Method Method: Test type: GLP: Year: Species/strain: Concentrations tested: Metabolic Activation: Remarks:	OECD: TG-473 <i>In vitro</i> mammalian chromosomal aberrations assay Yes 1999 Chinese hamster ovary cells (CHO) Up to 901 ug/ml (this level meets the 10 mM max. recommended level) Yes; Aroclor 1254-induced SD rat liver S9 The positive controls consisted of mitomycin-C and cyclophosphamide. Negative control was the test vehicle dimethylsulfoxide.
Results Result: Cytotoxic concentration: Precipitation concentration: Genotoxic effects With activation: Without activation: Statistical methods: Remarks:	No significant increases in cells with chromosomal aberrations, polyploidy, or endoreduplication were observed in the analyzed cultures at any concentration. >901 ug/ml (no signs of toxicity were noted) No precipitate was observed at the maximum concentration tested. Negative Negative Statistical analysis employed a Cochran-Armitage test for linear trends and Fisher's Exact Test to compare the percentage of cells with aberrations.
Conclusions	Material was not genotoxic (did not induce any structural or numerical aberrations) under conditions of this assay.
Data Quality Reliability: Remarks:	Reliable without restrictions This was a well-documented OECD guideline study conducted under GLP assurances.
References	Covance Laboratories Inc., Vienna, VA; Study number: 23080-0-437OECD; January 3, 2002.
Other	

E. Developmental Toxicity

Test Substance Test substance: Remarks:	MIPK Purity was >99%
Method Method: GLP: Year: Species/strain: Sex: Route of exposure: Exposure levels: Actual exposure levels: Exposure period: Frequency of treatment: Control group and treatment: Duration of test: Remarks:	OECD: TG-421; USEPA: OPPTS 870.3550 Yes 2001 Rats/Sprague-Dawley CRL:CD [®] (SD)IGS BR Male and Female (12/sex/exposure level) Inhalation, whole-body 0, 1, 2.5, and 5 mg/L 1.05 ± 0.046, 2.51 ± 0.144, and 5.17 ± 0.156 mg/L 6 hrs/day 7 days/week Controls were exposed to filtered room air Males were exposed for 51 days while females were exposed for 35 to 48 days (through Day 19 of gestation). The exposure period was initiated two weeks prior to mating, and continued during the two-week mating period. The male rats continued exposure for a total exposure of 51 days and the females were exposed until Day 19 of gestation. The study design included the additional endpoints of epididymal spermatozoan numbers and motility, and testicular spermatid head counts.
Results Maternal toxicity NOAEL:	Not Determined. Reductions in general activity levels were noted in all treated groups during the inhalation exposure. In addition, lower mean body weight gain and feed utilization was noted in all three treatment groups.
Repro./Develop. toxicity NOAEL:	1.0 mg/L. The effect noted in the 2.5 mg/L group was an increase in the number of dead pups/litter on lactation Day 0, an effect attributed to two of the twelve dams having three dead pups at birth. The mean percent Day 0 survival rate of the pups in the 2.5 mg/L group was 95.4%. Although this same effect was not noted in the 5.0 mg/L group, a reduced number of live pups/litter was noted on lactation Day 0 (mean of 11.6 versus 13.7 for the Control group) and an increased number of pups dying between lactation Days 0 to 4 (a 96.3% survival rate). The effect on lactation Day 0 (reduced number of live pups/litter) can be ascribed to one litter with 4 pups and the increased number of pups dying between lactation Days 0 to 4 is due to 4 pups dying in one litter during that time period. These differences were statistically significant due to the fact that the corresponding Control group had no litters with dead pups on lactation Day 0 and had no litters with any postnatal pup mortality.
Parental toxic responses:	Reductions in general activity levels during the inhalation exposure were noted the groups exposed to MIPK. Reductions in feed consumption, feed utilization, body weight and body weight gain were noted in the 2.5 and 5.0 mg/L groups. Lower mean body weight gain and feed utilization was noted at two time points for the male 1.0 mg/L group. Clinical signs noted in a groups exposed to MIPK included unkempt haircoat and saliva soaked perioral hair and periorcular porphyrin discharges were noted in the 2.5 and 5.0 mg/L groups. There was no effect on fertility or other endpoints related to reproductive performance in any treatment group.

Postnatal toxic responses:	<p>The only clinical signs considered related to exposure to the test article was a single pup in the 50 mg/L group that had loose, fluid-filled skin and hypothermia. The mean number of live pups/litter was reduced on lactation Day 0 and 4 for the 5.0 mg/L group. In addition, one litter in the 5.0 mg/L group had four pups die between Day 0 and 4. Two of twelve litters in the 2.5 mg/L group each had three dead pups on Day 0, with litter survival rates of 77-80%. Therefore, the number of dead pups/litter was increased for the 2.5 mg/L group although the pup survival rate was 95.4% (versus 100% in the Control group). The 1.0 mg/L group was comparable to the Control group.</p>
Statistical Methods:	<p>Homogeneity of data was evaluated using Bartlett's test ($p \leq 0.01$), one-way analysis of variance (ANOVA) ($p \leq 0.05$), and Dunnett's t-test ($p \leq 0.05$) to indicate statistical significance. When the variances of the means were not considered equal by the Bartlett's test ($p \leq 0.01$), the data were evaluated using a Kruskal-Wallis H-test ($p \leq 0.05$) followed by Mann-Whitney U-test ($p \leq 0.05$). The reproductive performance of the dams and the fertility and fecundity indices were evaluated in contingency tables, using a Chi-square test ($p \leq 0.05$). The total number of pups per litter (live and dead) and the total number of live pups per litter were evaluated using a linear regression model ($p \leq 0.05$).</p>
Remarks:	<p>MIPK did not affect the reproductive capacity of the adult animals in this study. Of the effects noted in the offspring, the reduced number of live pups/litter in the 5.0 mg/L is the most notable as the other effect noted at 5.0 mg/L (increased number of pups dying Day 0-4) was wholly dependent on one litter. The effect noted at 2.5 mg/L is of questionable significance given the propensity of dams to cannibalize and consume dead offspring. Finding three dead pups in two litters is unusual only in that dams usually consume the dead pups prior to them being found. These dead pups did not affect the mean number of live pups per litter or overall Day 0 survival rate (the mean value is also within the historical control range for this strain) and therefore this effect should be interpreted with caution.</p>
Conclusions	<p>Inhalation exposure to 1.0, 2.5, or 5.0 mg/L of MIPK resulted in significant toxicity to adult animals at all three exposure concentrations when compared to the control group. Fertility and other parameters related to reproductive capacity were unaffected in adult animals exposed to MIPK. The most significant effect (reduced mean number of pups/litter) on the offspring was noted at the 5.0 mg/L exposure level. The effect at 2.5 mg/L (increased number of dead pups/litter on Day 0) was of questionable significance as the number of live pups/litter and pup survival rate was unaffected. The 1.0 mg/L group was comparable to the Control group.</p>
Data Quality Reliability: Remarks:	<p>Reliable without restriction</p> <p>This was a well-documented OECD guideline study conducted under GLP assurances.</p>
References	<p>Reproduction/Developmental Toxicity Screening Test in the Rat. Toxicological Sciences Laboratory; Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study Number HAEL 2001-0250; Laboratory Project ID 200121, March 12, 2001.</p>
Other	

F. Toxicity to Reproduction

See robust summary E above which was a combined developmental/reproductive toxicity screening assessment.